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Paula S. Linkhart

Paula S. Linkhart

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Lydie Meheus
Reinhard Georg Lührmann
Ann Union
Joseph Raymackers

Serial No.:

Filed:

For: METHYLATED, SmD HOMOLOGOUS PEPTIDES, REACTIVE WITH THE ANTIBODIES FROM SERA OF LIVING BEINGS AFFECTED WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Group Art Unit:

Examiner:

Atty. Dkt. No.: INNS:011--1
11362.0011.DVUS01

PRELIMINARY AMENDMENT

BOX PATENT APPLICATION
Commissioner for Patents
Washington, DC 20231

Sir:

Prior to examination, please amend this application as follows:

IN THE SPECIFICATION:

At page 1, line 3, after the title, please insert the following new paragraph:

--This is a divisional of co-pending application Serial No. 09/297,981 filed May 10, 1999, which is a § 371 national application of PCT/EP98/05518 filed August 31, 1998, which claims priority under 35 U.S.C. § 119 to EP 97 870127.4 filed August 29, 1997.--

At page 3, line 30, please insert the heading:

--SUMMARY OF THE INVENTION--;

At page 7, after line 7, please insert the following headings and four paragraphs:

--BRIEF DESCRIPTION OF THE FIGURES

Figure 1: HPLC profile of the Endo-Lys digest.

Figure 2: Immunodot of HPLC fractions with 5 patients sera and 1 control serum.

Figure 3: Immunodot of the C-terminal peptide (C-term mod) and without (C-term nt mod) dimethylarginine, and of the recombinant (baculo SmD, coli SmD) and natural protein (native). Strips were incubated with an anti-SmD positive serum (+) and a control serum (-). Total protein staining (Aurodyne) was performed on the third strip.

Figure 4: LIA with modified (dimethyl arginine) C terminal peptide (fraction 15 from EndoLys-C digest, line 1 on the strip), and non-modified C terminal peptide (fraction 8 from the EndoLys-C digest, line 2 on the strip), both applied in equal amounts (60 ng). Additionally, 7, 15, and 30 ng of recombinant SmD1 from baculovirus- or E. Coli –infected insect cells (resp. 4, 5, 6 and 7, 8, 9) as well as 15 and 30 ng of a mixture of gel-purified SmD (native) were applied to the strips. The total protein staining (Aurodyne) was performed on the first strip. The strips were incubated with (A) a panel of anti-SmD positive sera selected by INNO-LIA ANA from ANF-positive sera, (B) a panel of anti-SmD positive sera selected by INNO-LIA ANA from a cohort of SLE patients

diagnosed according to the ACR criteria, (C) sera selected from the MCTD patients (control panel) and (D) sera selected from ANF-negative sera (control panel). No reactivity was observed with sera from the control panels.

DETAILED DESCRIPTION OF THE INVENTION--

At page 31, lines 6 through 27, please delete the heading "FIGURE LEGENDS" and the text describing the drawings.

At new page 48, please add the following:

--ABSTRACT

The present invention relates to a method of producing certain peptides containing methylated arginines that are followed by a glycine residue and that constitute immunogenic determinants of antibodies present in sera from patients with systemic lupus erythematosus, or Epstein-Barr virus, and wherein the methylation is a prerequisite for reacting with said antibodies. The invention also relates to the use of said peptides for diagnosis and treatment of systemic lupus erythematosus and related diseases, and diseases in which Epstein-Barr virus has been implicated.--

After the abstract (page 48), please insert the transferred SEQUENCE LISTING.

IN THE CLAIMS:

Please cancel claims 2-6, 10, and 14-22 without prejudice.

Please amend claims 1, 7-9 and 11-13 to read as follows:

1. (Amended) A peptide, that is either cyclized or branched, containing less than 50 amino acids, comprising at least one dimer of type XG, wherein X stands for an N^G-mono- or N^G-N^G-dimethylated arginine, asymmetrical dimethyl arginine, or N^G-N'^G-dimethylated arginine, symmetrical dimethyl arginine.

7. (Amended) A method for producing a peptide according to claim 1, by classical chemical synthesis, wherein methylated arginines are substituted for unmethylated arginine residues during the chemical synthesis.

8. (Amended) A method for producing a peptide according to claim 1, wherein the primary amino acid sequence is produced by classical chemical synthesis, and wherein the arginine residues that precede glycine residues are subsequently methylated by contacting said peptide with a protein arginine methyltransferase.

9. (Amended) A method for producing a peptide of claim 1 comprising the following steps:

-transforming an appropriate cellular host with a recombinant vector in which a polynucleic acid is inserted comprising the sequence that codes for said peptide or a protein under the control of the appropriate regulatory elements such that said peptide or a protein comprising said peptide is expressed and/or secreted;

-culturing said transformed cellular host under conditions allowing expression of said protein or peptide and allowing a partial or optimal methylation of the arginines present in said peptide; and

-harvesting said peptide.

11. (Amended) The method according to claim 9, wherein said host cell is a bacterial host or yeast or any other eukaryotic host cell which is preferably transformed with a recombinant baculovirus.

12. (Amended) An antibody raised upon immunization with a peptide according to claim 1, with said antibody being specifically reactive with the methylated forms of said peptide, and with said antibody being preferably a monoclonal antibody.

13. (Amended) An anti-idiotype antibody raised upon immunization with an antibody according to claim 12, with said anti-idiotype antibody specifically reactive with the antibody of claim 12.

Please add new claims 23-36 as follows:

--23. (New) The peptide of claim 1 that is specifically recognized by antibodies present in sera from patients with systemic lupus erythematosus (SLE), infectious, recurrent or chronic mononucleosis or infection, or certain cancers which are related to infection with Epstein-Barr virus.

24. (New) The peptide according to claim 1 comprising the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or an analog of any of SEQ ID NOs: 1-15, wherein the analog has an amino acid sequence identical to the respective SEQ ID NO except that the analog comprises conservative amino acid substitutions at one or more positions, where the conservative amino acid substitutions

are selected from the following: Thr, Gly, or Asn substituted for Ser; His, Lys, Glu, or Gln substituted for Arg; Ile, Met, Phe, Val, or Tyr substituted for Leu; Ala, Thr, or Gly substituted for Pro; Pro, Ser, Ala, Gly, His, or Gln substituted for Thr; Pro, Gly, or Thr substituted for Ala; Met, Ile, Tyr, Phe, or Leu substituted for Val; Ala, Thr, Pro, or Ser substituted for Gly; Met, Leu, Phe, Val, or Tyr substituted for Ile; Met, Tyr, Ile, Leu, Trp, or Val substituted for Phe; Phe, Trp, Met, Ile, Val, or Leu substituted for Tyr; Ser, Thr, or Met substituted for Cys; Gln, Arg, Lys, Glu, or Thr substituted for His; Glu, His, Lys, Asn, Thr, or Arg substituted for Gln; Asp, Ser, or Gln substituted for Asn; Arg, Glu, Gln, or His substituted for Lys; Asn, Glu, or Gln substituted for Asp; Gln, Asp, Lys, Asn, His or Arg substituted for Glu; and Ile, Leu, Phe, or Val substituted for Met.

25. (New) The peptide of claim 1 fused to a linker molecule.

26. (New) A peptide comprising tandem repeats of at least two of any of the peptides of claim 1.

27. (New) The method of claim 9 wherein the step of methylating arginine residues of said peptide is by contacting with a protein arginine methyltransfersase.

28. (New) The peptide of claim 1, covalently bound to a toxin molecule or active fragment thereof.

29. (New) The peptide of claim 1, wherein said peptide is suspended in a pharmaceutically acceptable vehicle.

30. (New) The antibody of claim 12, covalently bound to a toxin molecule or active fragment thereof.

31. (New) The antibody of claim 30, wherein said antibody is suspended in a pharmaceutically acceptable vehicle.

32. (New) A diagnostic kit for use in detecting antibodies which specifically bind SmD antigens, said kit comprising at least one peptide according to claim 1, with said peptide optionally bound to a solid support.

33. (New) The diagnostic kit according to claim 32, said kit comprising at least one peptide according to claim 1, optionally in combination with native methylated SmD1 or SmD3 and recombinant, unmethylated SmD1 or SmD3, wherein said peptides are attached to a solid substrate.

34. (New) The diagnostic kit according to claim 32 wherein said solid support is a membrane strip.

35. (New) The peptide according to claim 1 wherein X stands for N^G-mono- or N^G-N^G-dimethylated arginine.

36. (New) The peptide according to claim 1 comprising the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID NO: 15.--

REMARKS

I. Status of the Claims and Rationale for the Amendment

The parent application, U.S. Patent Application Serial No. 09/297,981, was allowed on November 05, 2001, but has not yet issued.

The specification has been amended to recite the relationship with the parent cases and to incorporate formalities required by the Examiner in the parent case. Support for the paragraphs inserted at page 7, line 7 is found at page 31, lines 6 through 27 of the original Specification.

Support for the Abstract added to page 48 is found on the cover page and at page 1, lines 5-12 of the original application PCT/EP98/05518, published as WO 99/11667.

The active claims in this case are claims 1, 7-9, and 11-13, as well as new claims 23-36. The new claims 23-36 are directed to peptides, methods of producing peptides and kits containing peptides for use in diagnosing auto-immune diseases. These new claims find support in the original claims of Serial No. 09/297,981, as shown in the table below. A **Marked Up Set of Claim Amendments** is attached.

New Claim	*Original Claim Supporting New Claims*
23	1, 4, 6
24	1, 2, 4, 6
25	3, 4, 6
26	5, 4, 6
27	10, 4, 6
28	14, 4, 6
29	15, 4, 6
30	14, 4, 6
31	15, 4, 6
32	19, 4, 6
33	20, 4, 6
34	21, 4, 6
35	1, 4, 6
36	1, 2, 4, 6

II. Sequence Listing

Attached please find the sequence information, including the computer readable form previously submitted in the co-pending application Serial No. 09,297,981, filed May 10, 1999, for use in this application, in accordance with the sequence Rules under 37 C.F.R. § 1.821(e).

It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct said fees from Deposit Account No. 01-2508/11362.0011.DVUS01.

Respectfully submitted,

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Date: January 24, 2002

MARKED UP VERSION OF CLAIM AMENDMENTS

1. (Amended) A [Peptide] peptide, that is either cyclized or branched, containing less than 50 amino acids, comprising at least one dimer of type XG, wherein X stands for an N^G-mono- or N^G-N^G-dimethylated arginine, asymmetrical dimethyl arginine, or N^G-N'^G-dimethylated arginine, symmetrical dimethyl arginine [~~that is able to react with antibodies and with, said methylation being crucial for the reaction between said peptide and said antibodies and wherein said antibodies are present in sera from patients with: systemic lupus erythematosus, or infectious, recurrent or chronic mononucleosis or infection, or certain cancers which are related to infection with Epstein Barr virus, such as Burkitt's lymphoma or nasopharyogeal carcinoma~~].

7. (Amended) A [~~Method~~] method for producing a peptide according to [~~any of claims 1 to 6~~] claim 1, by classical chemical synthesis, wherein methylated arginines are substituted for unmethylated arginine residues during the chemical synthesis.

8. (Amended) A [~~Method~~] method for producing a peptide according to [~~any of claims 1 to 6~~] claim 1, wherein the primary amino acid sequence is produced by classical chemical synthesis, and wherein the arginine residues that precede glycine residues are subsequently methylated by contacting said peptide with a protein arginine methyltrasferase.

9. (Amended) A [~~Method~~] method for producing a peptide of [~~any of claims 1 to 6~~] claim 1 comprising the following steps:

-transforming an appropriate cellular host with a recombinant vector in which a polynucleic acid is inserted comprising the sequence that codes for said peptide or a

protein under the control of the appropriate regulatory elements such that said peptide or a protein comprising said peptide is expressed and/or secreted[,];

-culturing said transformed cellular host under conditions allowing expression of said protein or peptide and allowing a partial or optimal methylation of the arginines present in said peptide[,]; and

-harvesting said peptide.

11. (Amended) [~~Method~~] The method according to [~~any of claims 9 or 10~~] claim 9, wherein said host cell is a bacterial host or yeast or any other eukaryotic host cell which is preferably transformed with a recombinant baculovirus.

12. (Amended) An antibody raised upon immunization with a peptide according to [~~any of the claims 1 to 6~~] claim 1, with said antibody being specifically reactive with the methylated forms of said peptide, and with said antibody being preferably a monoclonal antibody.

13. (Amended) An [~~Anti-idiotype~~] anti-idiotype antibody raised upon immunization with an antibody according to claim 12, with said anti-idiotype antibody being specifically reactive with the antibody of claim 12 [~~, thereby mimicking the methylated form of a peptide according to any of claims 1 to 6, and with said antibody being preferably a monoclonal antibody~~].

23. (New) The peptide of claim 1 that is specifically recognized by antibodies present in sera from patients with systemic lupus erythematosus (SLE), infectious, recurrent or chronic mononucleosis or infection, or certain cancers which are related to infection with Epstein-Barr virus.

24. (New) The peptide according to claim 1 comprising the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or an analog of any of SEQ ID NOs: 1-15, wherein the analog has an amino acid sequence identical to the respective SEQ ID NO: except that the analog comprises conservative amino acid substitutions at one or more positions, where the conservative amino acid substitutions are selected from the following: Thr, Gly, or Asn substituted for Ser; His, Lys, Glu, or Gln substituted for Arg; Ile, Met, Phe, Val, or Tyr substituted for Leu; Ala, Thr, or Gly substituted for Pro; Pro, Ser, Ala, Gly, His, or Gln substituted for Thr; Pro, Gly, or Thr substituted for Ala; Met, Ile, Tyr, Phe, or Leu substituted for Val; Ala, Thr, Pro, or Ser substituted for Gly; Met, Leu, Phe, Val, or Tyr substituted for Ile; Met, Tyr, Ile, Leu, Trp, or Val substituted for Phe; Phe, Trp, Met, Ile, Val, or Leu substituted for Tyr; Ser, Thr, or Met substituted for Cys; Gln, Arg, Lys, Glu, or Thr substituted for His; Glu, His, Lys, Asn, Thr, or Arg substituted for Gln; Asp, Ser, or Gln substituted for Asn; Arg, Glu, Gln, or His substituted for Lys; Asn, Glu, or Gln substituted for Asp; Gln, Asp, Lys, Asn, His or Arg substituted for Glu; and Ile, Leu, Phe, or Val substituted for Met.

25. (New) The peptide of claim 1 fused to a linker molecule.

26. (New) A peptide comprising tandem repeats of at least two of any of the peptides of claim 1.

27. (New) The method of claim 9 wherein the step of methylating arginine residues of said peptide is by contacting with a protein arginine methyltransfersase.

28. (New) The peptide of claim 1, covalently bound to a toxin molecule or active fragment thereof.

29. (New) The peptide of claim 1, wherein said peptide is suspended in a pharmaceutically acceptable vehicle.

30. (New) The antibody of claim 12, covalently bound to a toxin molecule or active fragment thereof.

31. (New) The antibody of claim 30, wherein said antibody is suspended in a pharmaceutically acceptable vehicle.

32. (New) A diagnostic kit for use in detecting antibodies which specifically bind SmD antigens, said kit comprising at least one peptide according to claim 1, with said peptide optionally bound to a solid support.

33. (New) The diagnostic kit according to claim 32, said kit comprising at least one peptide according to claim 1, optionally in combination with native methylated SmD1 or SmD3 and recombinant, unmethylated SmD1 or SmD3, wherein said peptides are attached to a solid support.

34. (New) The diagnostic kit according to claim 32 wherein said solid support is a membrane strip.

35. (New) The peptide according to claim 1 wherein X stands for N^G-mono- or N^G-N^G-dimethylated arginine.

36. (New) The peptide according to claim 1 comprising the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, or SEQ ID NO: 15.